LIÈGE université
GIGA
Consciousness

When consciousness fades away

Lessons from noncommunicating states

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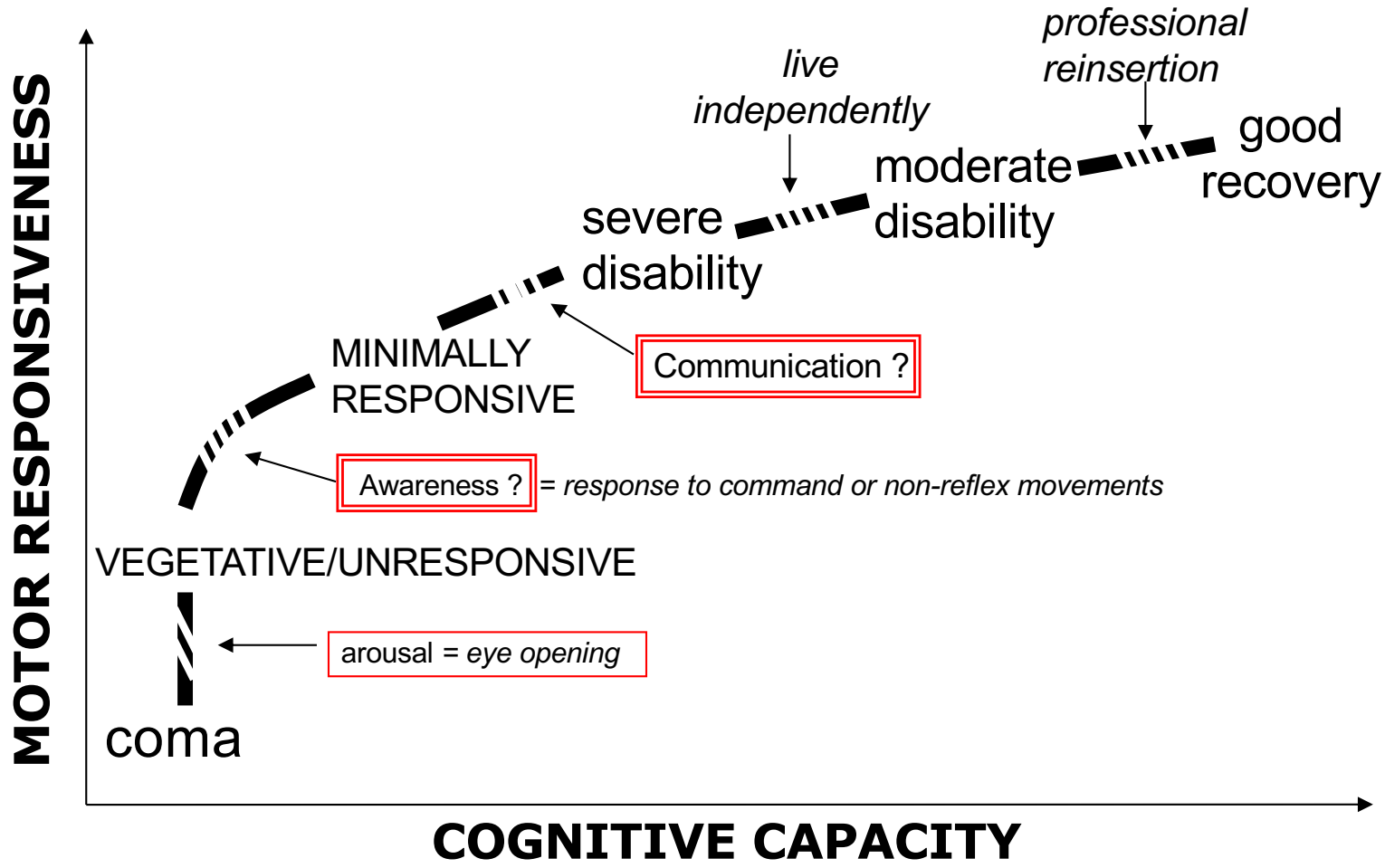
CHU de Liège
Inserm Institut national de la santé et de la recherche médicale
esa European Space Agency
Human Brain Project
James S. McDonnell Foundation

Consciousness in real-life

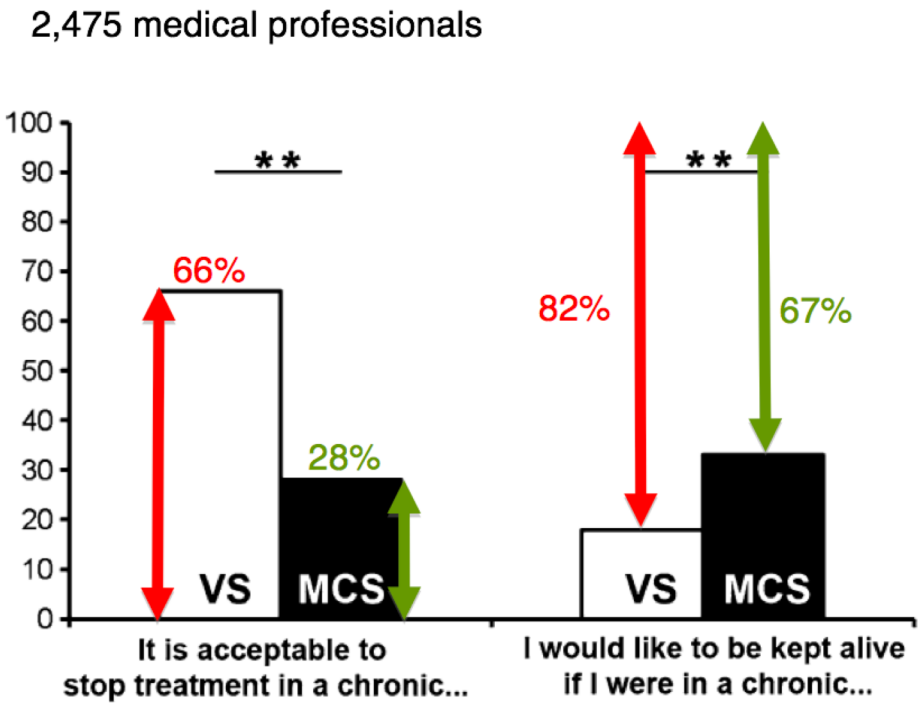
Terri Schiavo °1963,
cardiac arrest, vegetative 1990, † 2005 USA

Behavioural signs of Consciousness

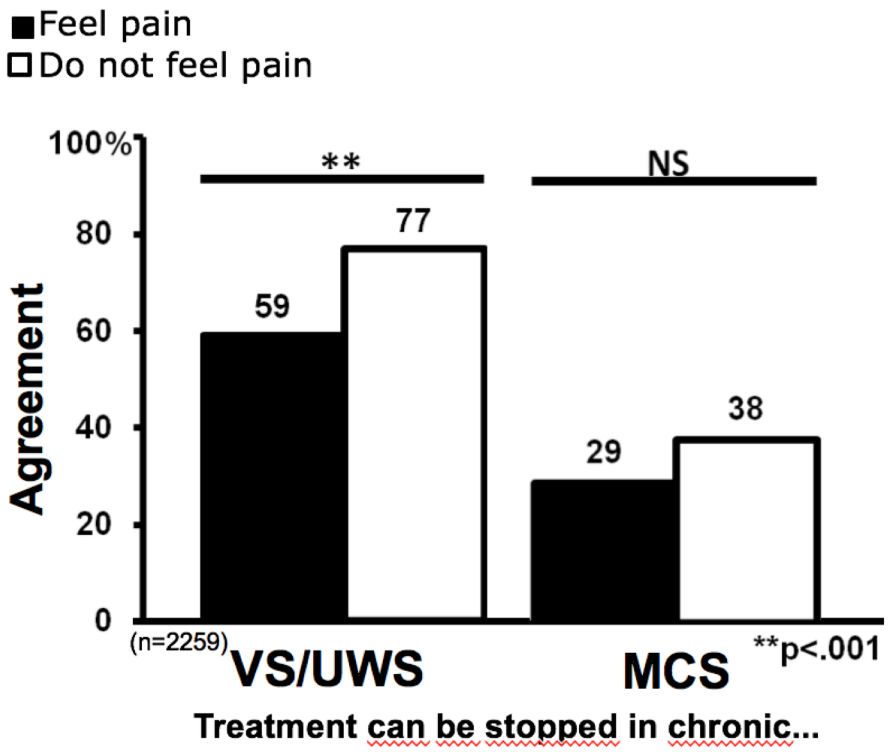


Laureys et al, *Curr Opin Neurol* 2005

Not everyone agrees with guidelines



Demertzi et al, *J Neurol* 2011



Demertzi et al, *Prog Brain Res* 2009
Demertzi & Racine et al, *Neuroethics* 2012

We cannot always trust behavior

Standardized assessment

n=103 post-comatose patients

45 Clinical diagnosis of VS
18 Coma Recovery Scale MCS

⇩

40% misdiagnosed

Schnakers et al, *Ann Neurol* 2006; *BMC Neurol* 2009

JFK COMA RECOVERY SCALE - REVISED ©2004

Record Form

This form should only be used in association with the "CRS-R ADMINISTRATION AND SCORING GUIDELINES" which provide instructions for standardized administration of the scale.

Patient:	Diagnosis:	Etiology:
Date of Onset:	Date of Admission:	

Date															
Week	ADM	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
AUDITORY FUNCTION SCALE																
4 - Consistent Movement to Command *																
3 - Reproducible Movement to Command *																
2 - Localization to Sound																
1 - Auditory Startle																
0 - None																
VISUAL FUNCTION SCALE																
5 - Object Recognition *																
4 - Object Localization: Reaching *																
3 - Visual Pursuit *																
2 - Fixation *																
1 - Visual Startle																
0 - None																
MOTOR FUNCTION SCALE																
6 - Functional Object Use †																
5 - Automatic Motor Response *																
4 - Object Manipulation *																
3 - Localization to Noxious Stimulation *																
2 - Flexion Withdrawal																
1 - Abnormal Posturing																
0 - None/Flaccid																
OROMOTOR/VERBAL FUNCTION SCALE																
3 - Intelligible Verbalization *																
2 - Vocalization/Oral Movement																
1 - Oral Reflexive Movement																
0 - None																
COMMUNICATION SCALE																
2 - Functional: Accurate †																
1 - Non-Functional: Intentional *																
0 - None																
AROUSAL SCALE																
3 - Attention																
2 - Eye Opening w/o Stimulation																
1 - Eye Opening with Stimulation																
0 - Unarousable																
TOTAL SCORE																

Denotes emergence from MCS†

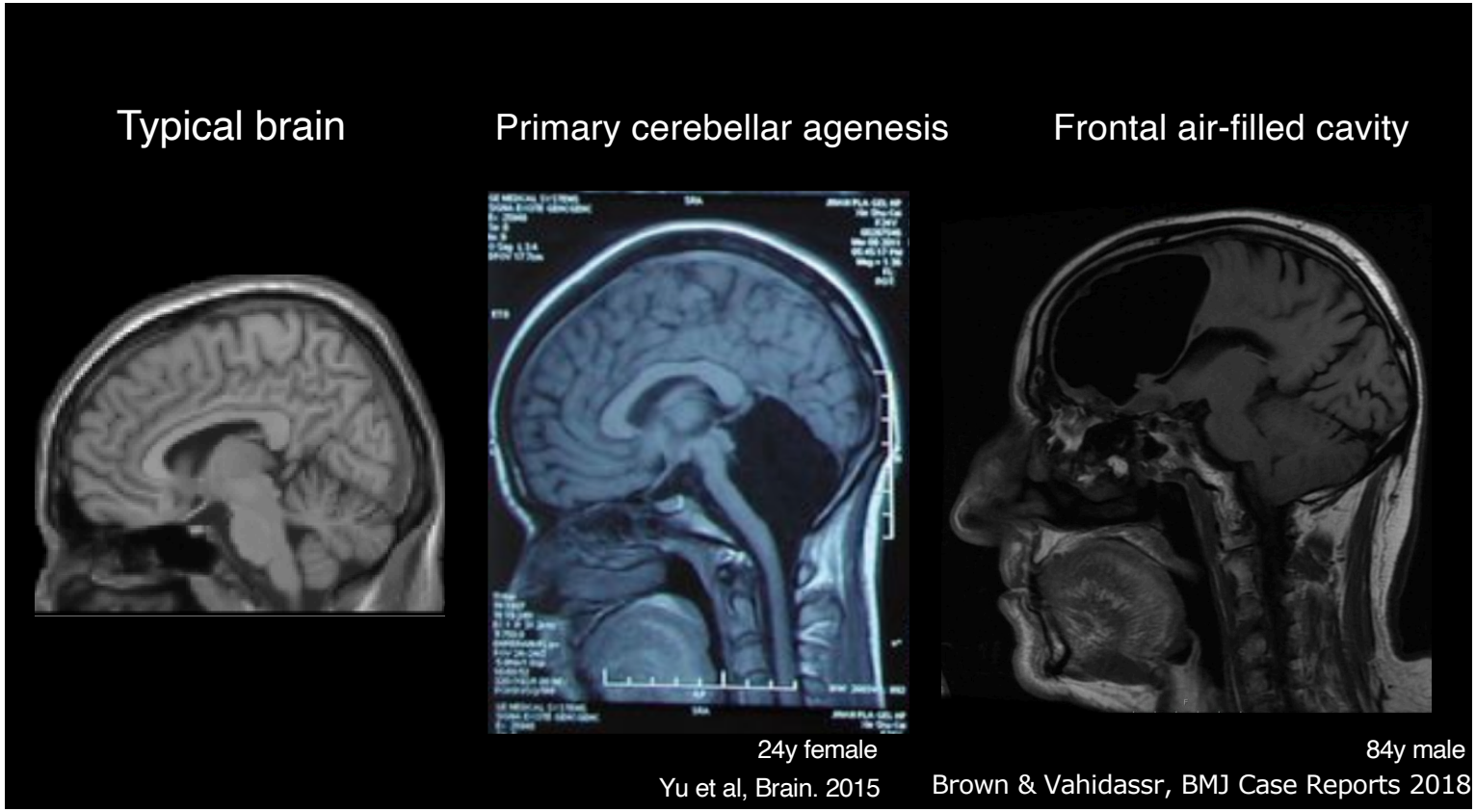
Denotes MCS *

1

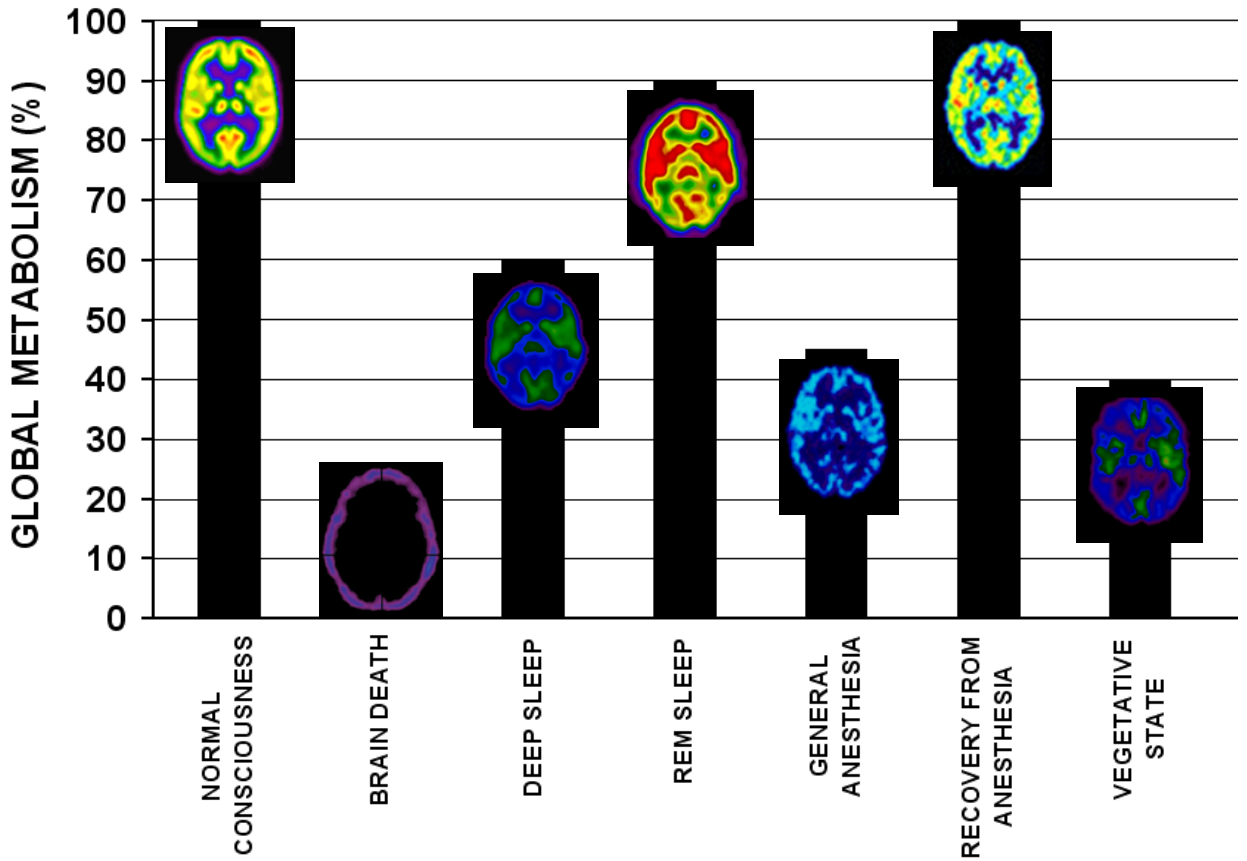
Giacino et al, *Neurology* 2002

To be conscious, we need a brain

(all of it?)



To be conscious, we need a *functional* brain

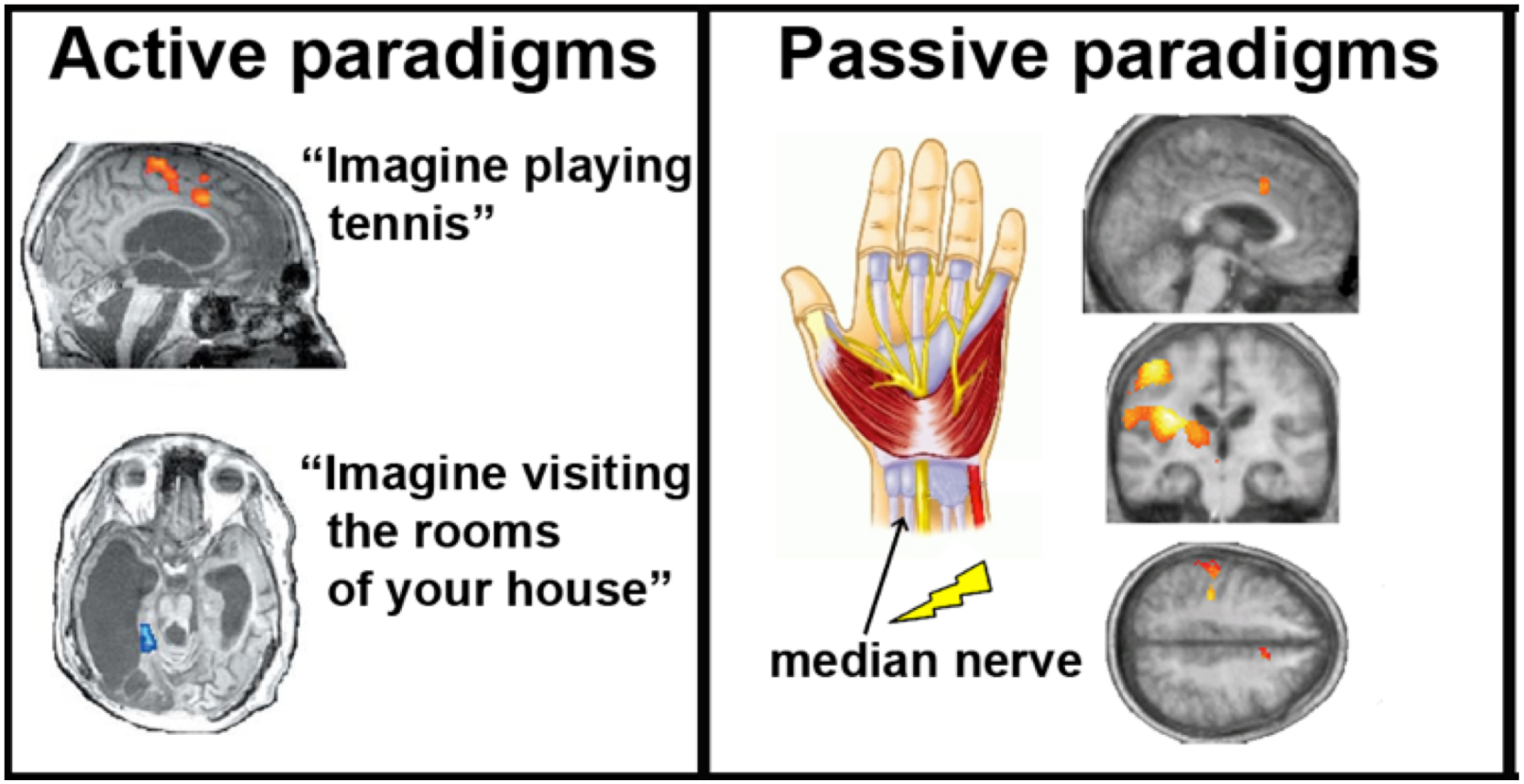


Laureys et al., Lancet Neurology, 2004
(sleep data from Pierre Maquet; anesthesia data from Mike Alkire)

Neuroimaging paradigms

Owen et al, Science 2006
Monti & Vanhaudenhuyse et al, NEJM 2010

Boly et al, Lancet Neurol 2008

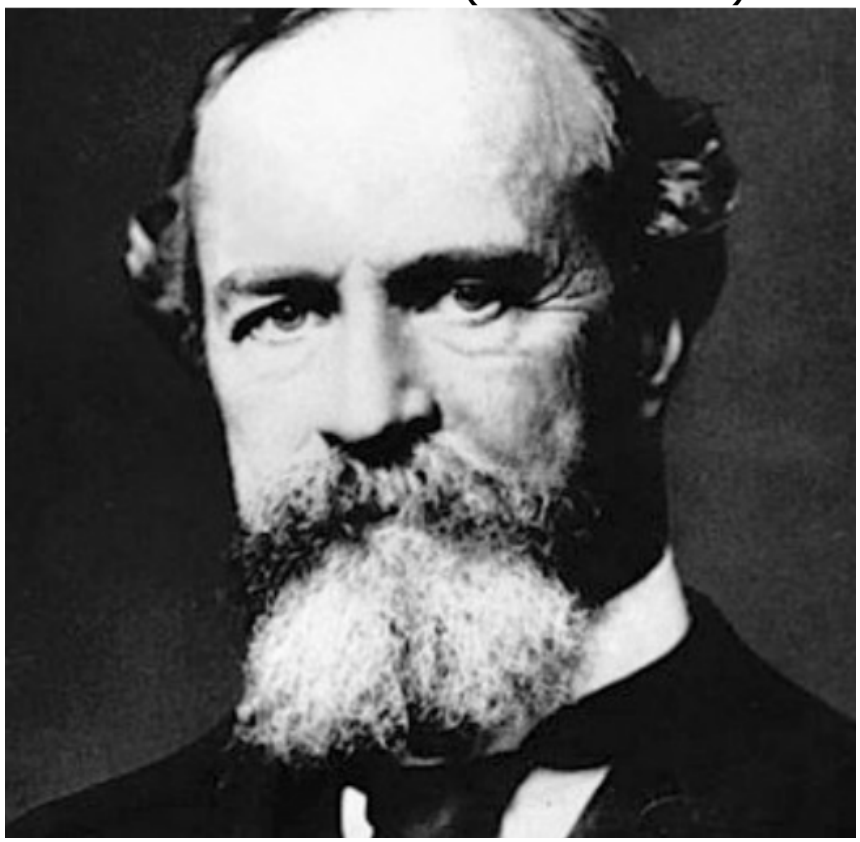


Heine, Di Perri, Soddu, Laureys, Demertzi
In: *Clinical Neurophysiology in Disorders of Consciousness,* Springer-Verlag 2015

Demertzi & Laureys, In: *I know what you are thinking: brain imaging and mental privacy*, Oxford University Press 2012

The stream of consciousness

William James (1842-1910)



The stream of thought (Chapter IX)

The principles of psychology 1890

Some numbers…

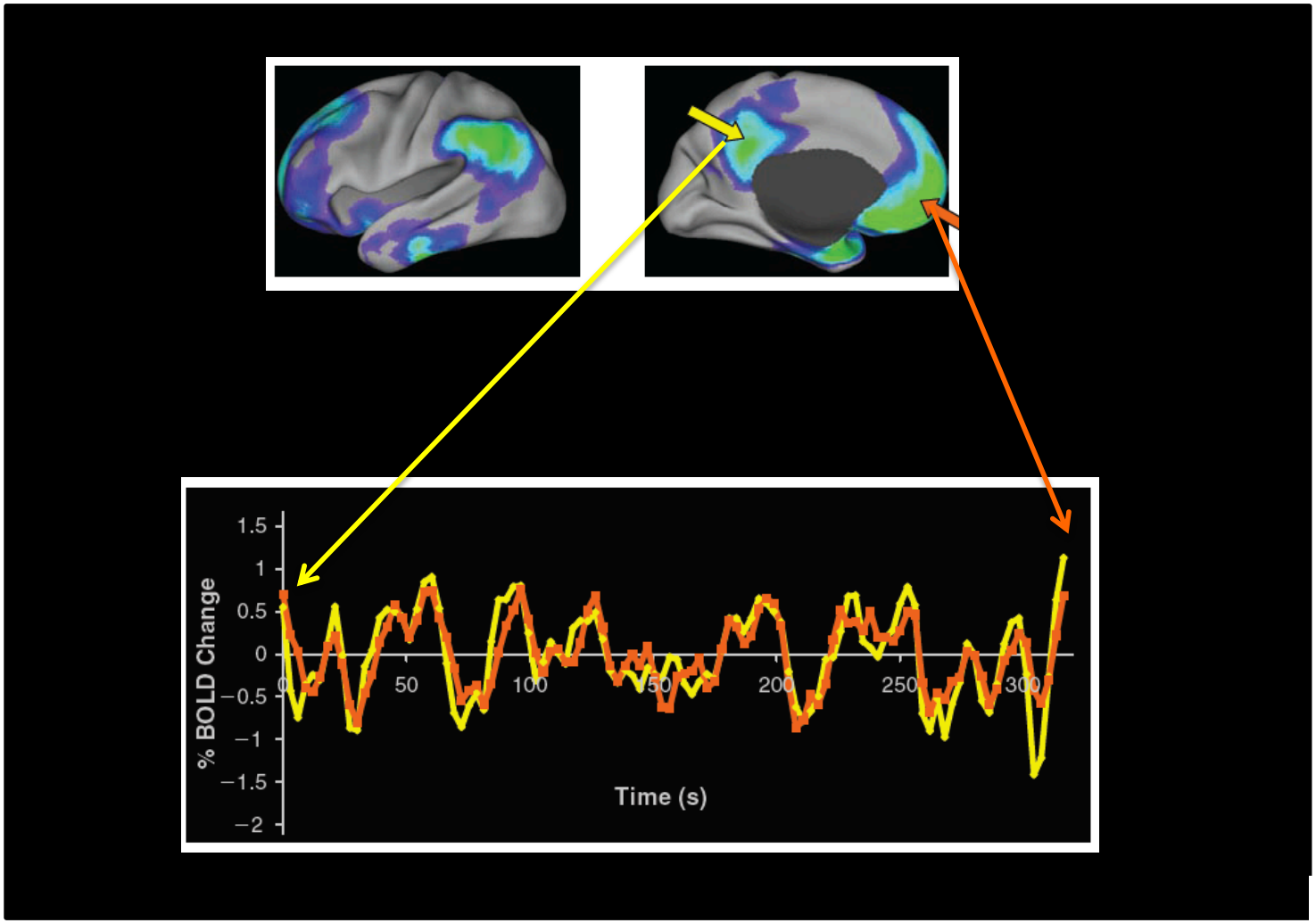
- The human brain is approximately 2% of body's weight
- 80% of this energy for neuronal signalling
  → most of consumed energy used for function
- Stimulus & performance-evoked changes in brain energy consumption are surprisingly small (typically <5%)

While conscious awareness is a low bandwidth phenomenon and therefore energetically inexpensive, it is dependent upon a very complex, dynamically organized, non-conscious state of the brain that is achieved at great expense

Raichle & Snyder. Intrinsic Brain Activity and Consciousness. In: Laureys S, Tononi G, editors. The Neurology of Consciousness. Oxford: Elsevier Academic Press; 2009. p. 81-48

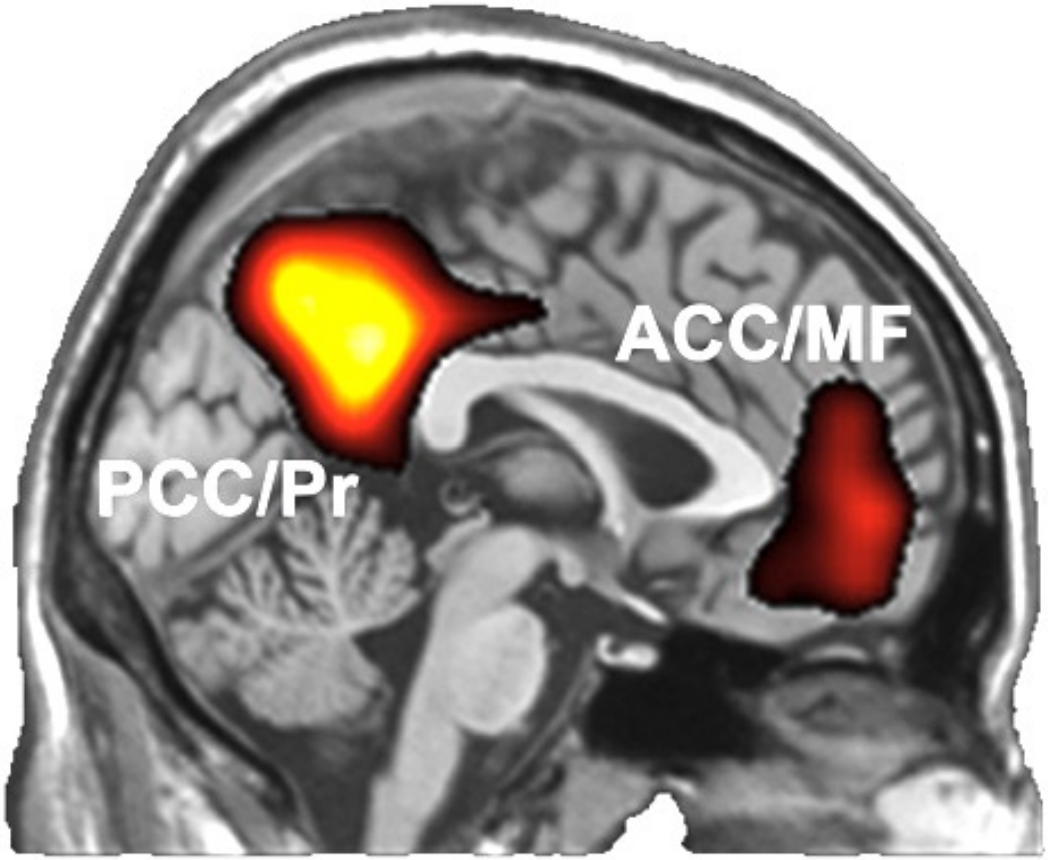
Task deactivations

Task performance - Rest (fixation/eyes closed) → **Deactivations**



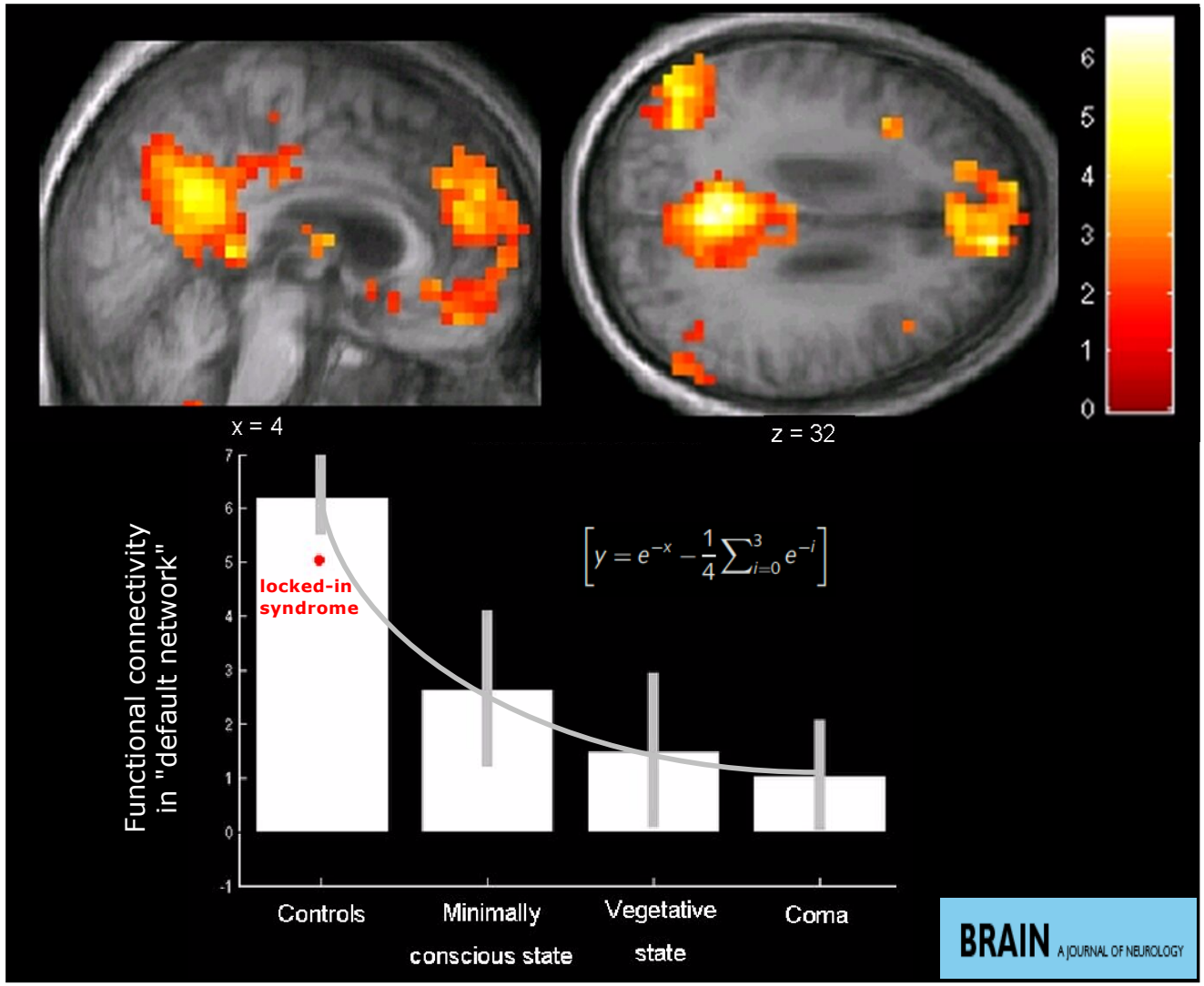
Raichle & Snyder. Intrinsic Brain Activity and Consciousness. In: Laureys S, Tononi G, editors. The Neurology of Consciousness. Oxford: Elsevier Academic Press; 2009. p. 81-48

The brain's default mode at rest



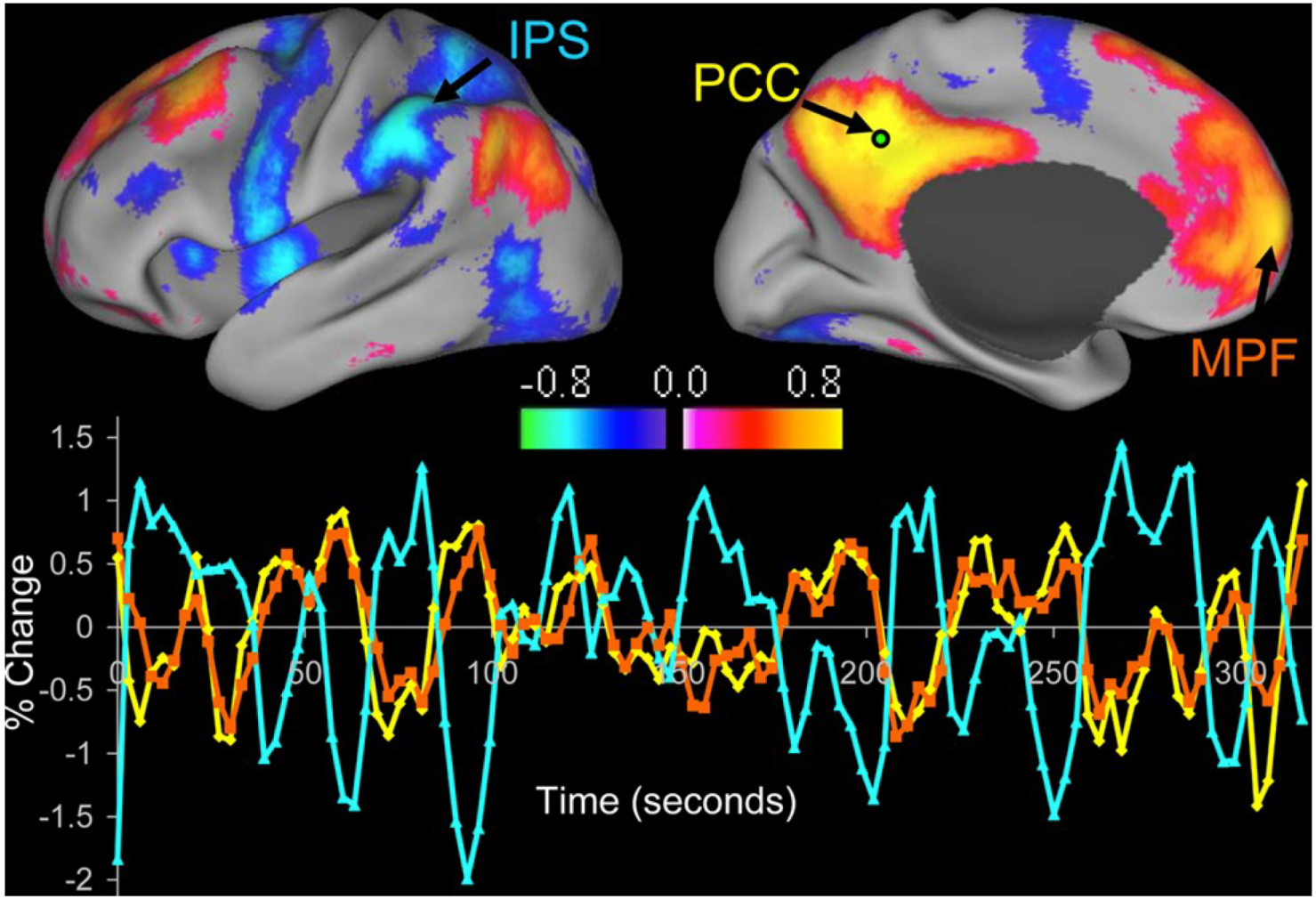
Demertzi & Whitfield-Gabrieli, in: Neurology of Consciousness 2nd ed. 2015
Demertzi, Soddu, Laureys, *Curr Opin Neurobiology* 2013
Demertzi et al, *Front Hum Neurosci* 2013
Raichle et al, *PNAS* 2001

Default mode network in DOC



Vanhaudenhuyse & Noirhomme et al, *Brain* 2010

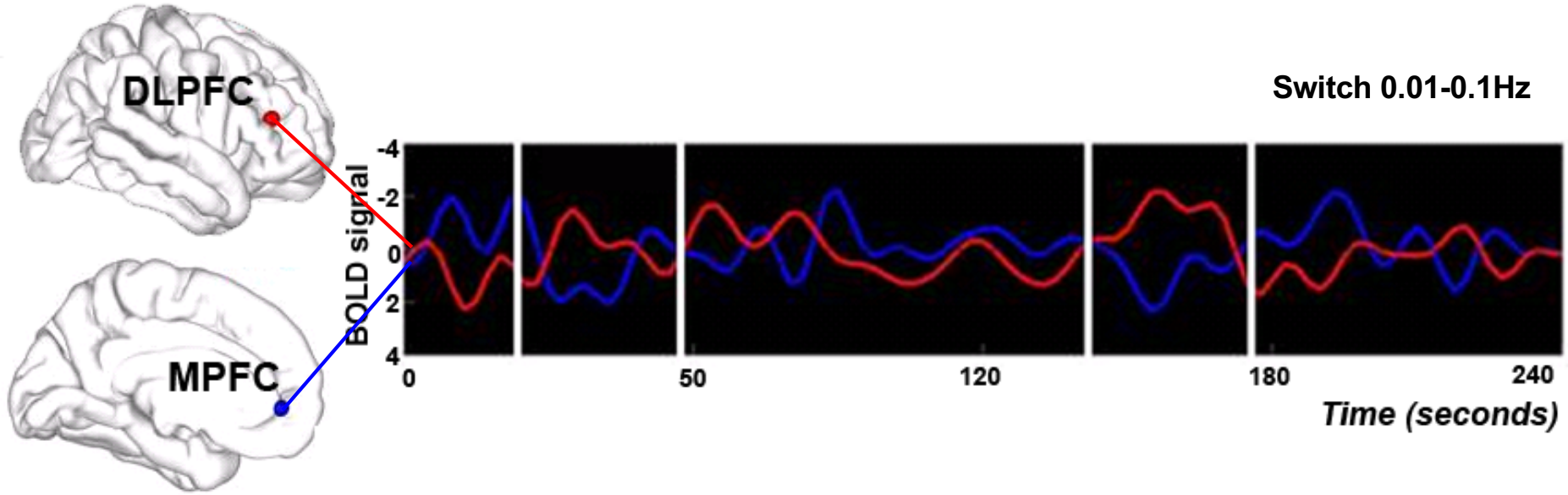
DMN anticorrelations



Fox et al, *PNAS* 2005

DMN anticorrelations

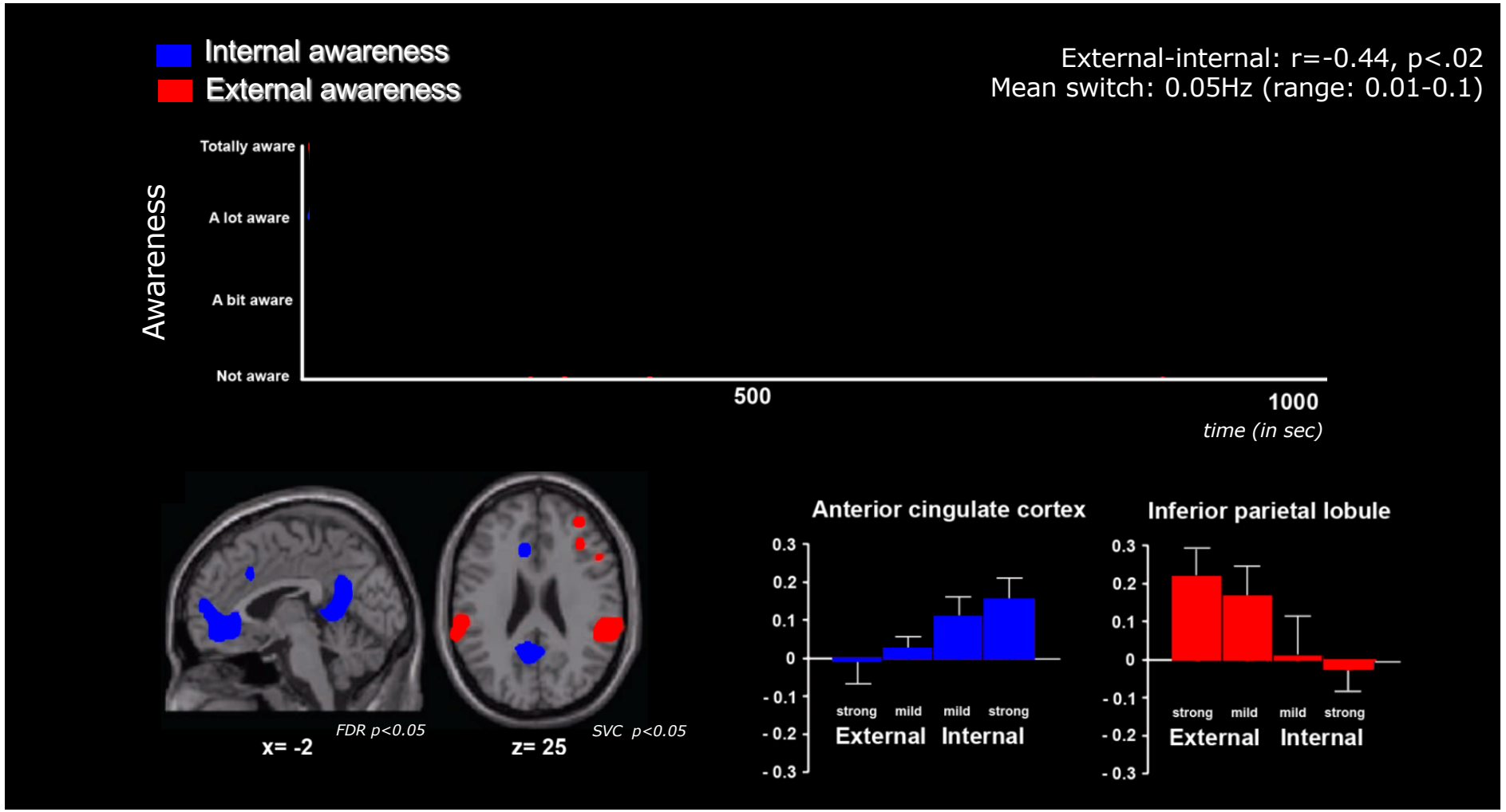
External awareness
***or* anticorrelated network**



Internal awareness
***or* Default mode network**

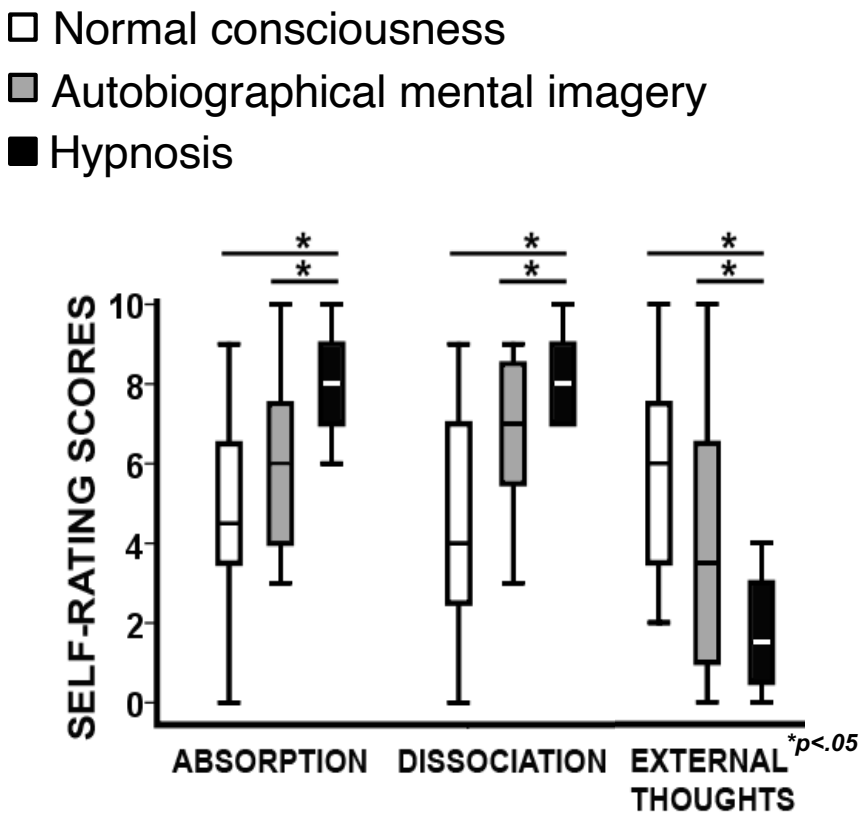
Demertzi & Whitfield-Gabrieli, in: *Neurology of Consciousness* 2nd ed. *2015*
Demertzi, Soddu, Laureys, *Curr Opin Neurobiology* 2013
Demertzi et al, *Front Hum Neurosci* 2013

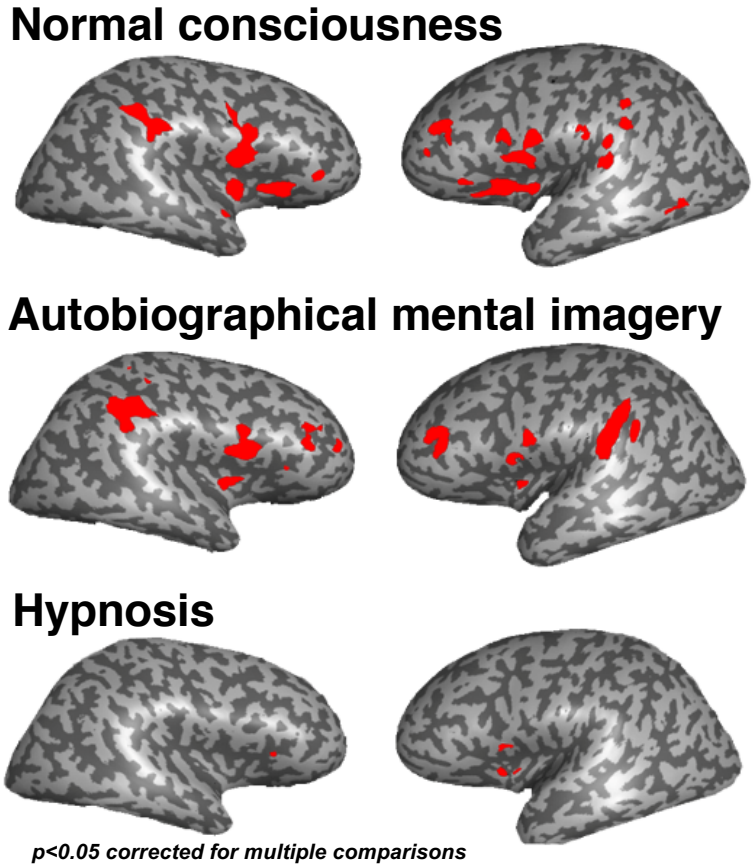
Cognitive-behavioral relevance



Vanhaudenhuyse*, Demertzi* et al, *J Cogn Neurosci* 2011

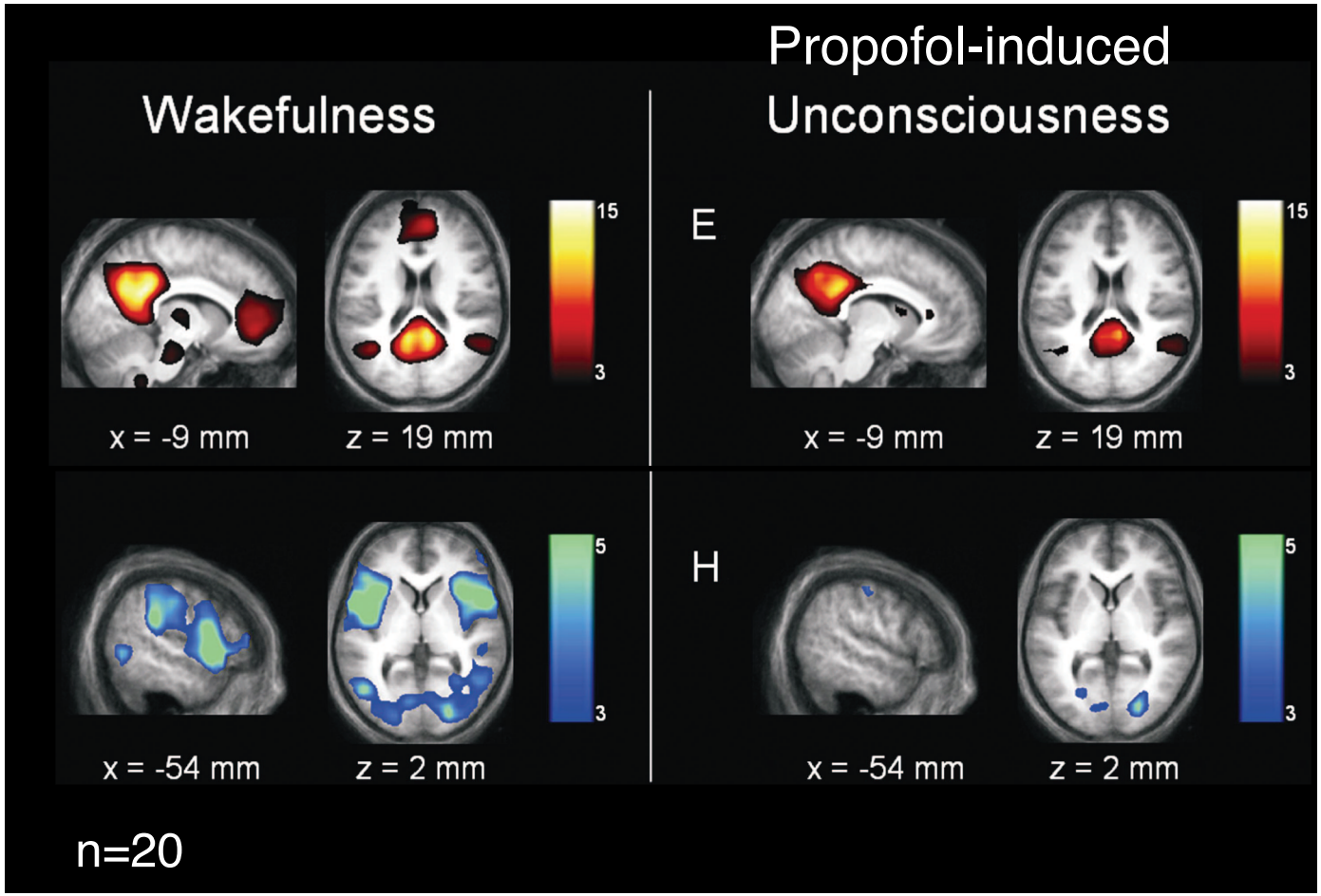
Anticorrelations and awareness





Demertzi, Soddu, Faymonville et al, *Prog Brain Res* 2011
Demertzi, Vanhaudenhuyse, Noirhomme, Faymonville, Laureys, *J Physiol Paris* 2015

Anticorrelations and wakefulness

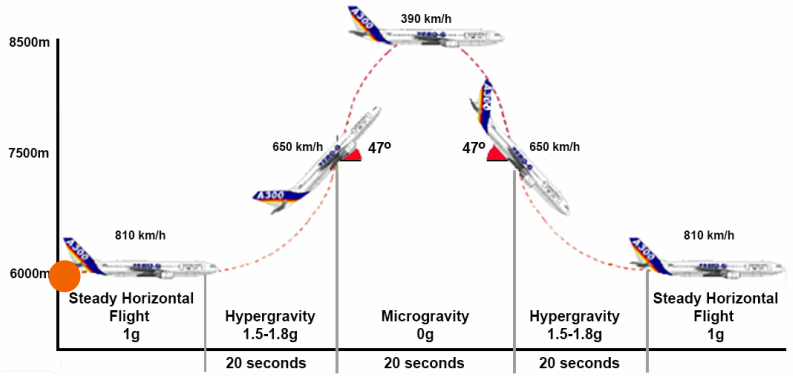


Boveroux et al, *Anesthesiology* 2010

Effect of environment

SCIENTIFIC REPORTS
www.nature.com/scientificreports/

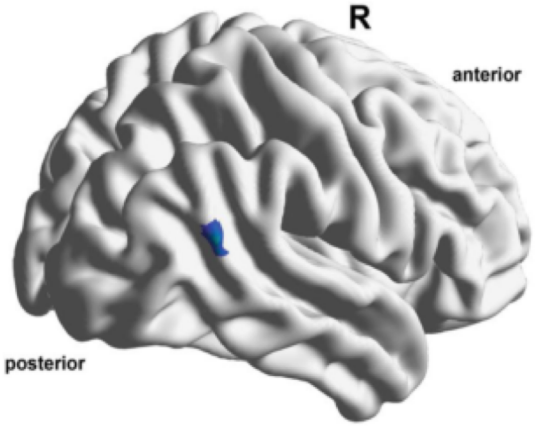
Parabolic flight

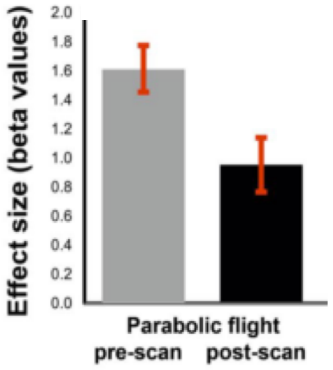


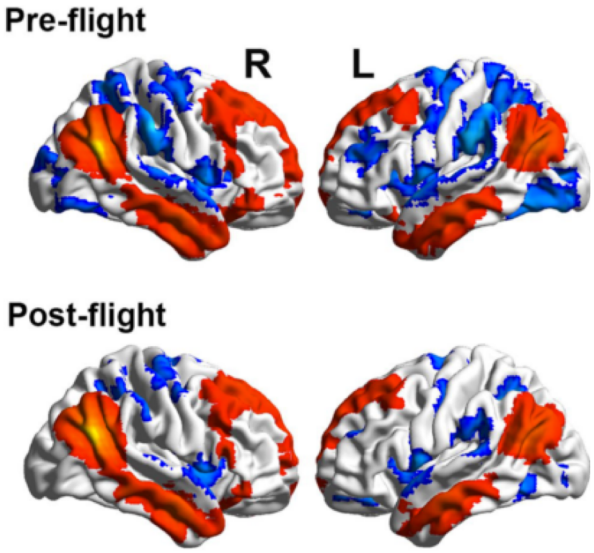
Parabolic flight trajectory

Angelique Van Ombergen[1], Floris L. Wuyts[1], Ben Jeurissen[2], Jan Sijbers[2], Floris Vanhevel[3], Steven Jillings[1], Paul M. Parizel[3], Stefan Sunaert[4], Paul H. Van de Heyning[1], Vincent Dousset[5], Steven Laureys[6] & Athena Demertzi[6,7]

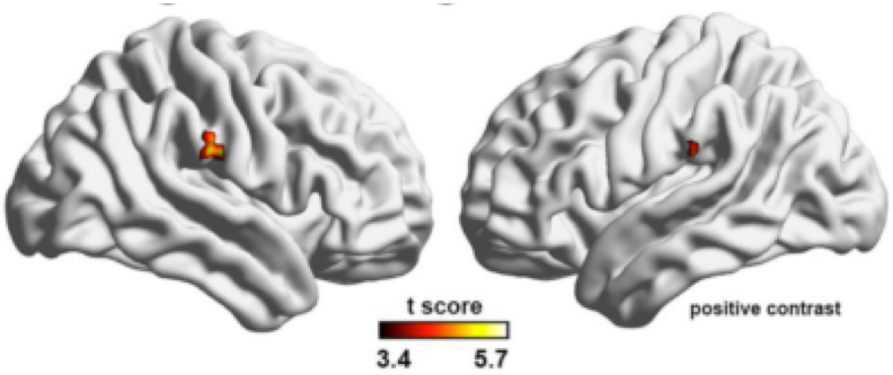
Anticorrelations and environment

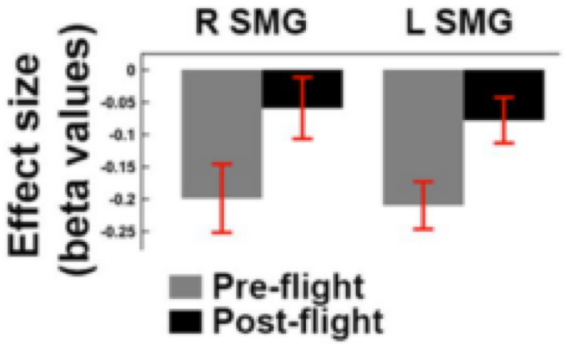






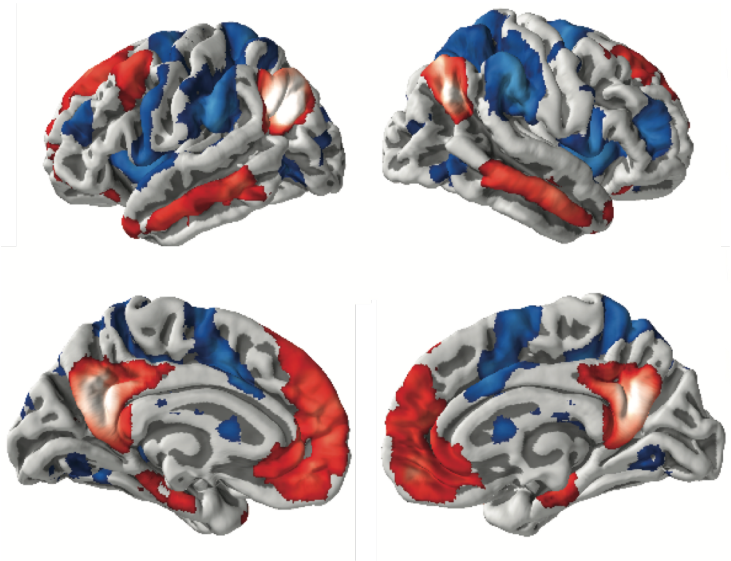
Post – Pre flight

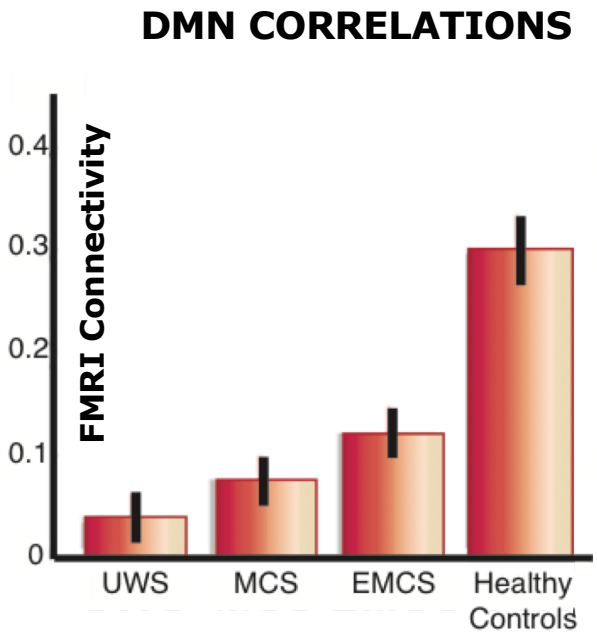


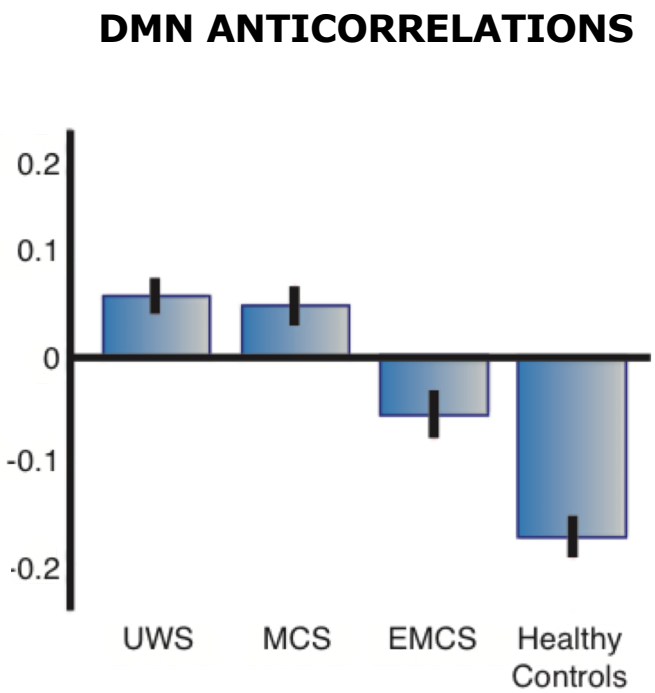


Van Ombergen … and Demertzi, *Sci Reports* 2017
Demertzi et al, *Brain Str Funct* 2015

Anticorrelations and pathology

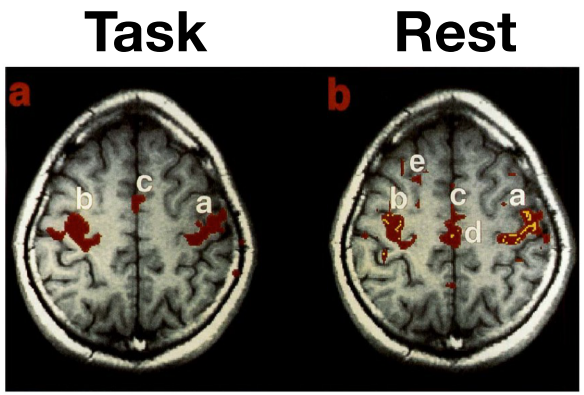




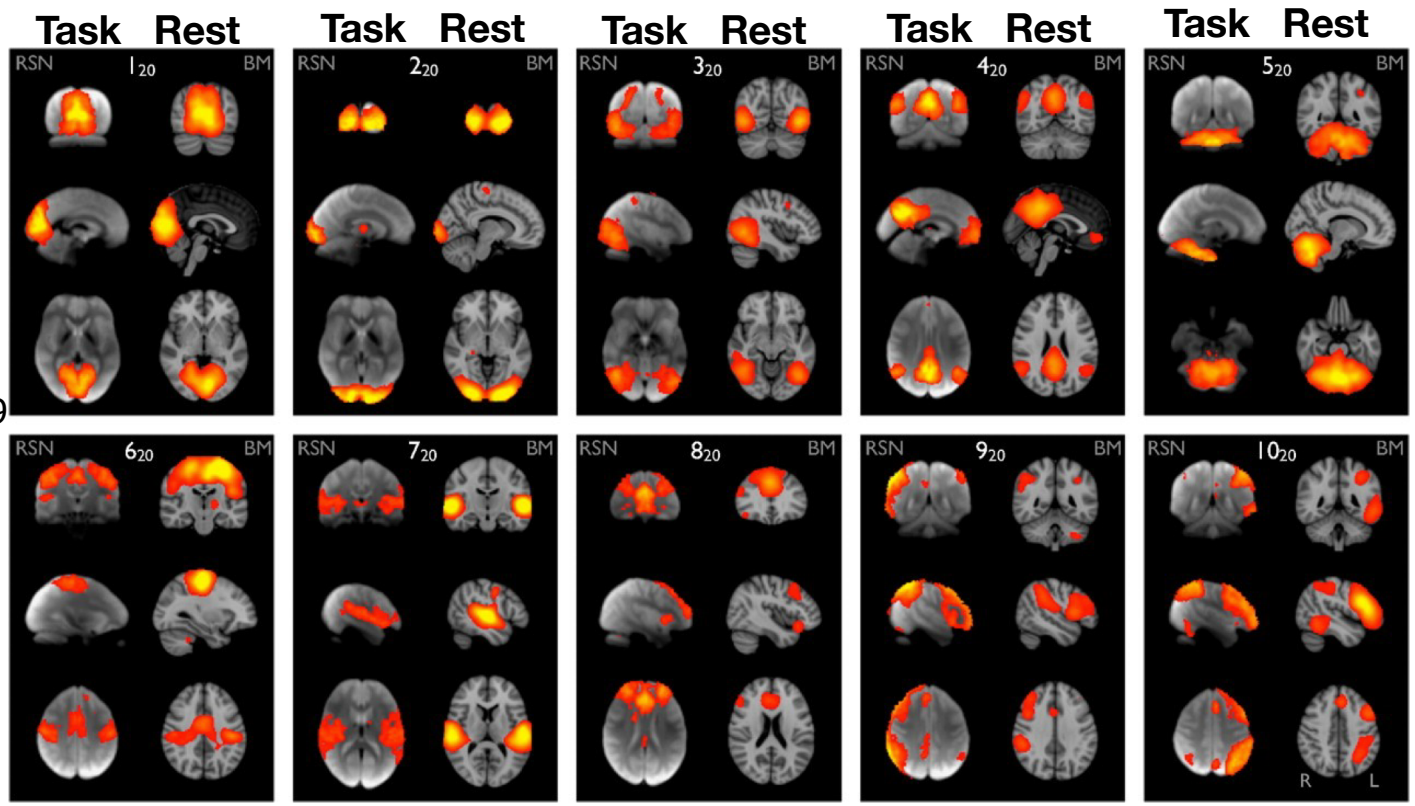


Di Perri, …, Demertzi*, Laureys*, Soddu*, *Lancet Neurol* 2017
Vanhaudenhuyse et al, *Brain* 2010

Many resting state networks

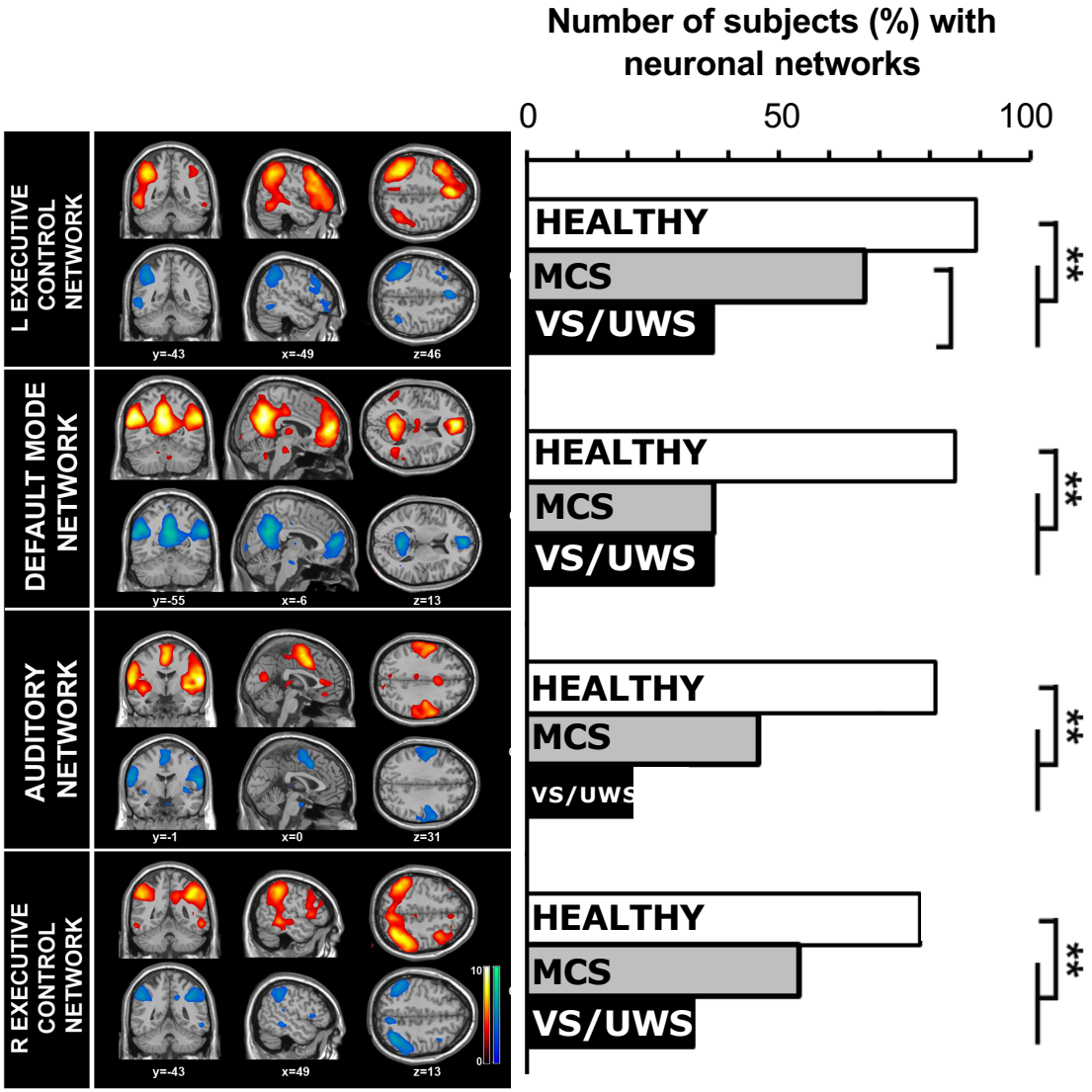


Biswal et al., *Magn. Reson. Med*.19



Smith et al, *PNAS* 2009

Network connectivity disrupted



Single-patient classification

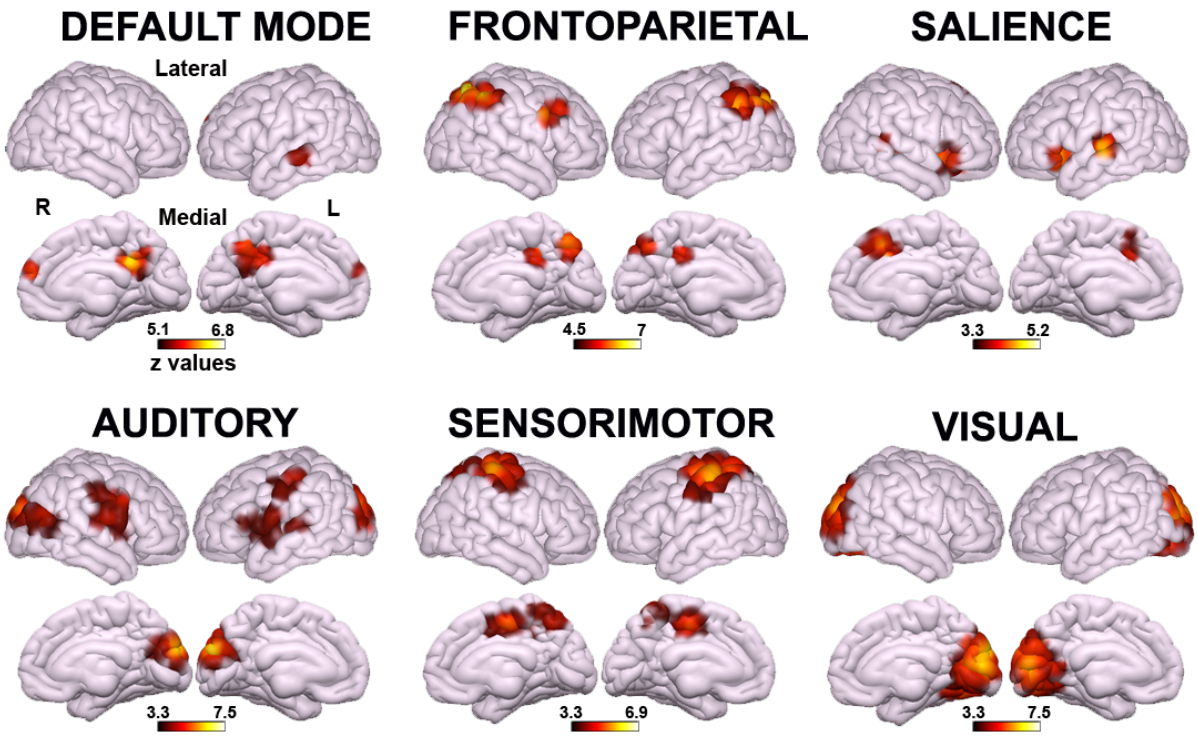
Performance measures	Accuracy	TPR healthy	TPR patients	Selected RSNs
	Healthy vs. all patients			
Neuronal	85.3	.82	.87	Auditory, DMN

Demertzi & Gómez et al, *Cortex* 2014

Heine et al, *Front Psychol* 2012; Smith et al, *PNAS* 2009; Beckmann et al, *Phil. Trans. R. Soc. B* 2005

Which network discriminates best?

MCS> VS/UWS



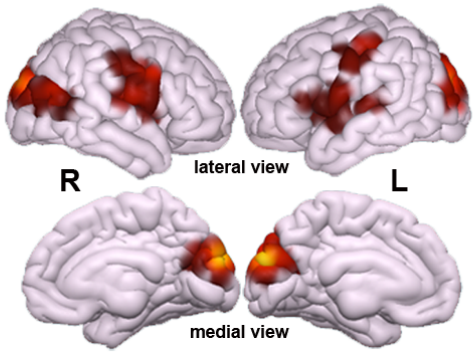
	Feature selection criterion (t-test)			Single-feature classification		
Network	**t value**	**Rank**	**p value**	**TP MCS**	**TN VS/UWS**	**Accuracy**
Auditory	8.32	1	<.001	25	18	43/45
Visual	7.79	2	<.001	23	15	38/45
Default mode	6.95	3	<.001	23	15	38/45
Frontoparietal	6.82	4	<.001	23	15	38/45
Salience	6.21	5	<.001	24	15	39/45
Sensorimotor	5.87	6	<.001	24	13	37/45

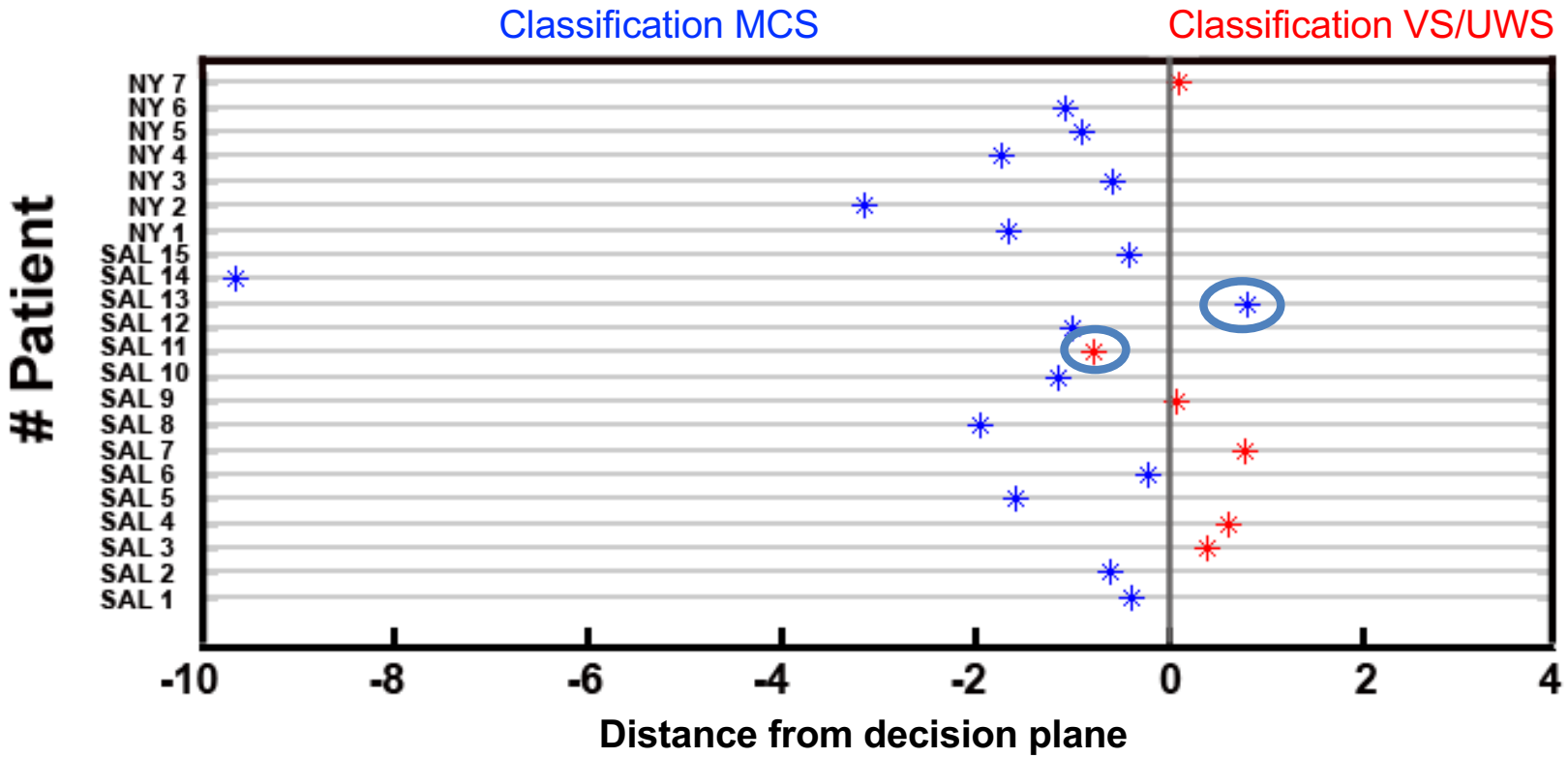
FWE p<0.05 (cluster-level)

Demertzi & Antonopoulos et al, *Brain* 2015

Crossmodal connectivity classifies DOC

- Training set: 45 DOC (26 MCS, 19 VS/UWS)
  - 14 trauma, 28 non-trauma, 3 mixed
  - 34 patients assessed >1m post-insult
- Test set: **16 MCS**, **6 VS/UWS** (M_{age}: 43y, 15 non-trauma; all chronic), from 2 different centers





Demertzi & Antonopoulos et al, *Brain* 2015

Stationary connectivity

RS stationary connectivity :

- is linked to behavior and task performance *(Laird et al,. J Cogn Neurosci 2011)*
- reflects physiological & pathological unconsciousness *(Heine et al, Front Psychol 2012)*
- permits single-patient automatic diagnosis (*Demertzi & Antonopoulos et al, Brain 2015)*

But

it remains unclear to what extent it provides a representative estimate of cognition

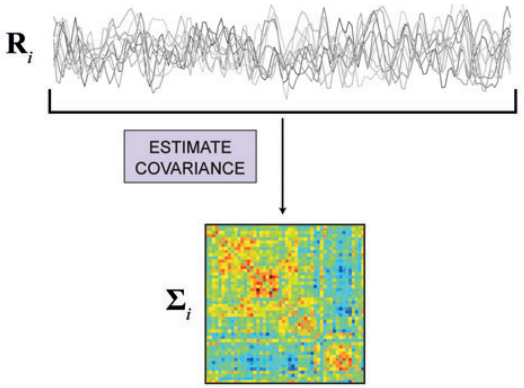
(*Peterson et al, NeuroImage Clin* 2015)

Ongoing interactions among distinct brain regions

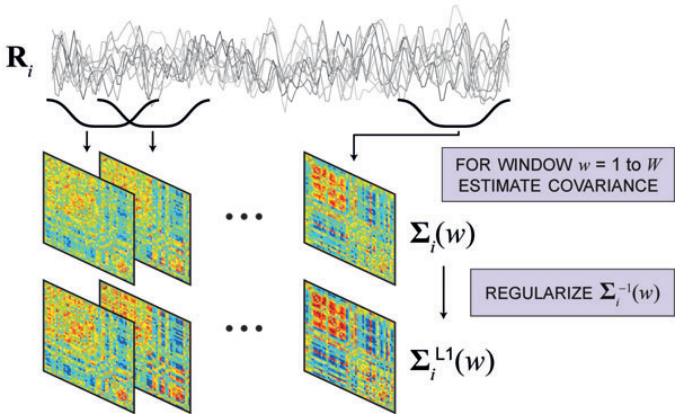
(Hutchison et al, NeuroImage 2013)

From stationarity to dynamics

Stationary fc



Time-varying fc



Dynamic

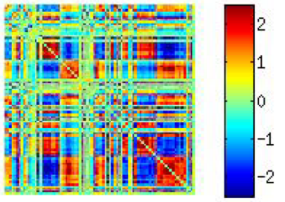
$$x_t = A \cdot x_{t-1} + \epsilon_t$$

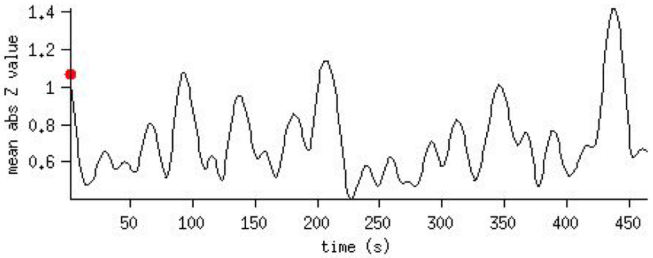
Allen et al, *Cereb Cortex* 2014
Liegeois et al, *Nat Communications* 2019

Brain dynamics and cognition

Typical wakefulness: significance for performance, emotion and cognition

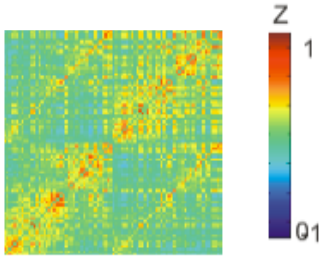
(Alavash et al, *Neuroimage*, 2016; Shine et al *Neuron*, 2016; Friston *Neuroimage*, 1997; Thompson et al, *Hum Brain Mapp,* 2013)





Unconsciousness: rigid spatiotemporal organization, less metastable dynamics

- sleep (Tagliazucchi et al, *PNAS* 2013; Wang et al, *PNAS* 2016; Wilson et al., *Neuroimage* 2015; Chow et al, *PNAS* 2013)
- anesthesia
  - in humans (Tagliazucchi et al, *J. R. Soc. Interface* 2016; Kafashan et al, *Front Neural Circuits*, 2016; Amico et al, *PLoS One* 2014)
  - in animals (Barttfeld et al, *PNAS* 2014); Grandjean et al, *Neuroimage* 2017; Liang et al, *Neuroimage* 2015).

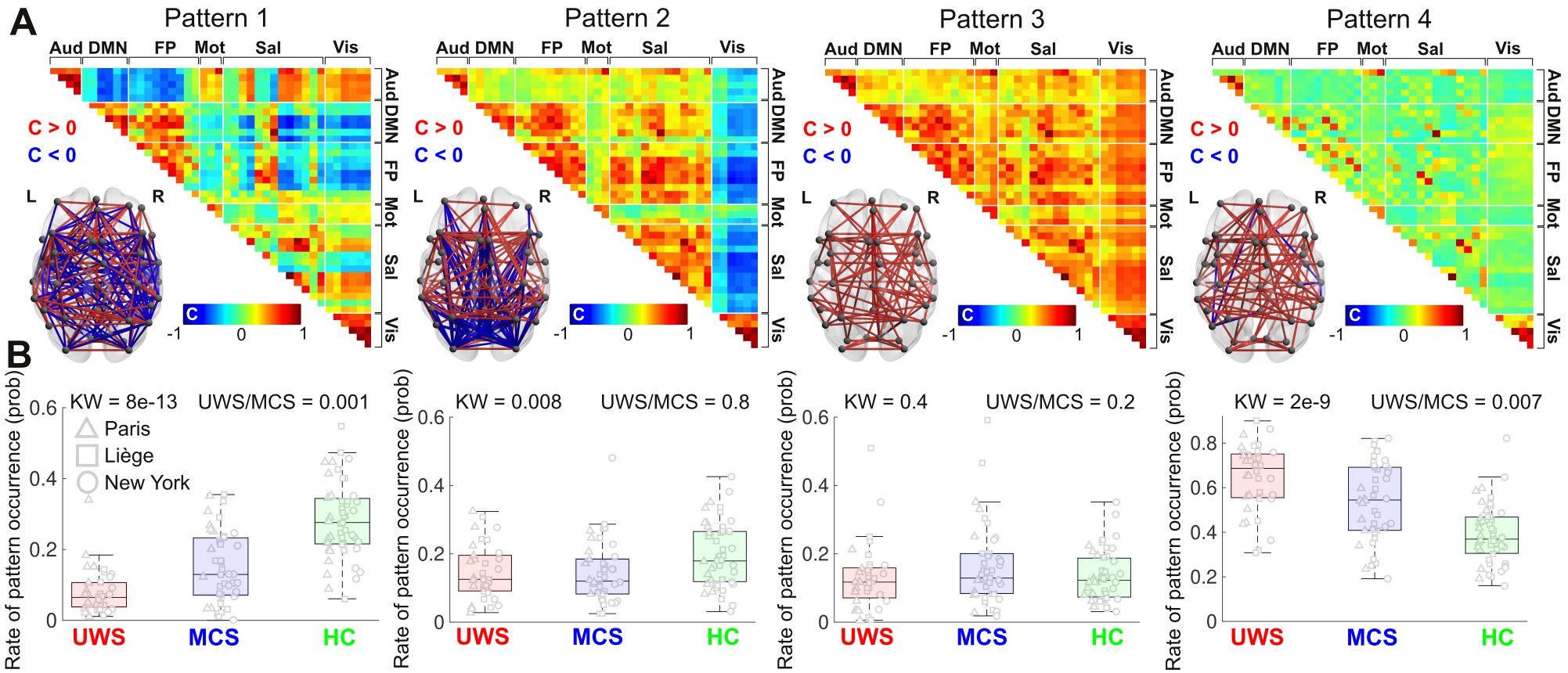


Barttfeld*, Ulhrig*, Sitt*, et al, *PNAS* 2015

The brain cannot map the complexity of the internal and external world

(Dehaene et al, *Trends Cog Sci, 2006;* Tononi et al, *Nat Rev Neurosci.* 2016)

Patterns of recurrent coordinated activity



Demertzi & Tagliazucchi, Dehaene, Deco, Barttfeld, Raimondo, Martial, Fernández-Espejo, Rohaut, Voss, Schiff, Owen, Laureys, Naccache, Sitt.
Science Advances 2019

More chances to transition if in higher conscious state

Markov Process

- *stochastic process that has no memory*
- *selection of next state depends only on current state, and not on prior states*
- *process is fully defined by a set of transition probabilities* π_{ij}

  π_{ij} = probability of selecting state j next, given that presently in state i.

  Transition-probability matrix Π collects all π_{ij}

Transition-Probability Matrix

O Example

- *system with three states*

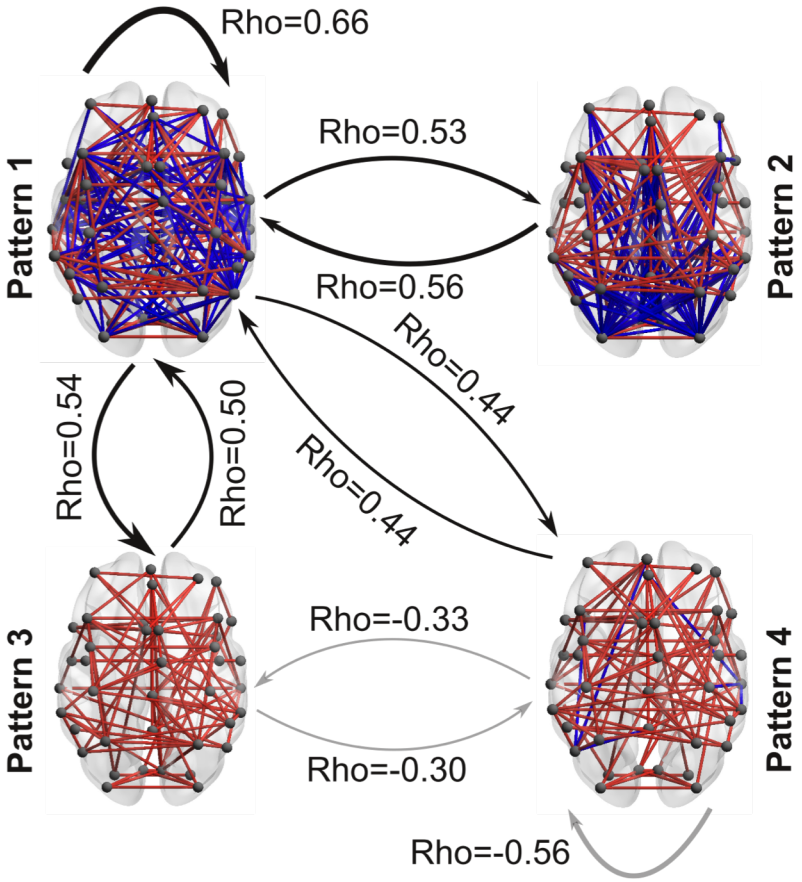
If in state 1, will stay in state 1 with probability 0.1

If in state 1, will move to state 3 with probability 0.4

Never go to state 3 from state 2

$$\Pi \equiv \begin{pmatrix} \pi_{11} & \pi_{12} & \pi_{13} \\ \pi_{21} & \pi_{22} & \pi_{23} \\ \pi_{31} & \pi_{32} & \pi_{33} \end{pmatrix} = \begin{pmatrix} 0.1 & 0.5 & 0.4 \\ 0.9 & 0.1 & 0.0 \\ 0.3 & 0.3 & 0.4 \end{pmatrix}$$

Consciousness-level dependent



Demertzi & Tagliazucchi, Dehaene, Deco, Barttfeld, Raimondo, Martial, Fernández-Espejo, Rohaut, Voss, Schiff, Owen, Laureys, Naccache, Sitt. *Science Advances* 2019

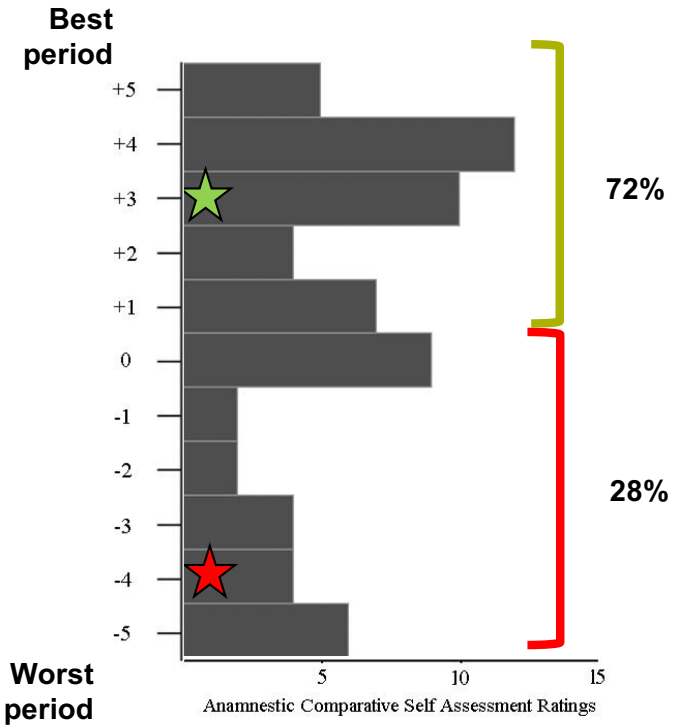
Why does it matter?

Balancing costs-benefits

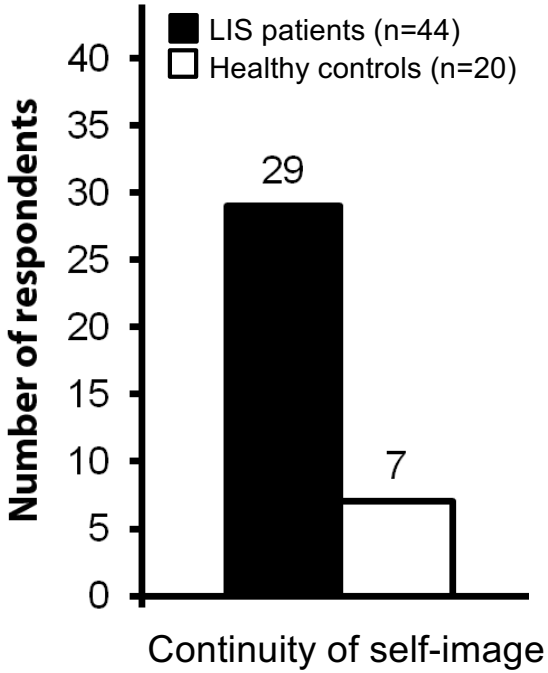
Results of Tests	Beneficial Effects	Harmful Effects
- brain activity than neurological examination	Relatives: decisions to limit life-sustaining treatment	Relatives: may lose hope, purpose, and meaning in life
+ brain activity than neurological examination	Clinical management: may be intensified by the chance of further recovery	Relatives: false hopes
Same as neurological examination	Clinicians & relatives: may be affirmed in their decision about the level of treatment	Clinicians & relatives: may be disappointed & treatment cost/effectiveness may be poor

Jox, Bernat, Laureys, Racine, *Lancet Neurology* 2012

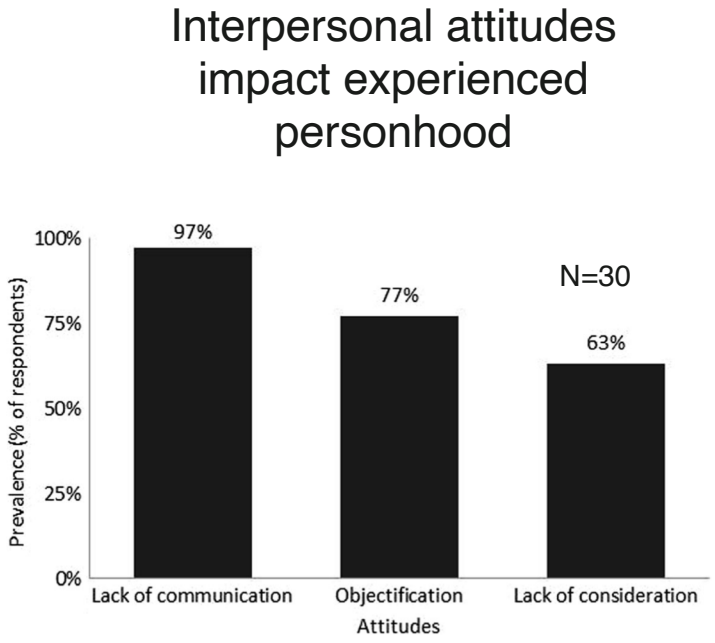
Quality of Life



Bruno et al, *Br Med J Open* 2011



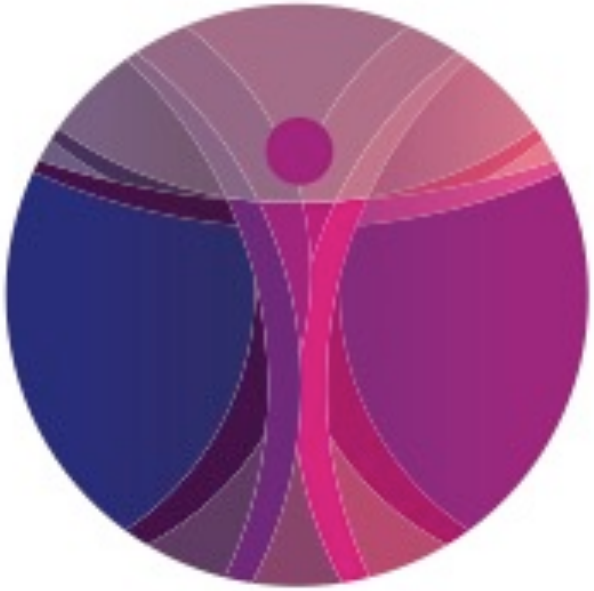
Nizzi & Demertzi et al, *Conscious & Cogn* 2012



Nizzi, Blandin, Demertzi *NeuroEthics* 2018

ALIS
Association du Locked-in Syndrome

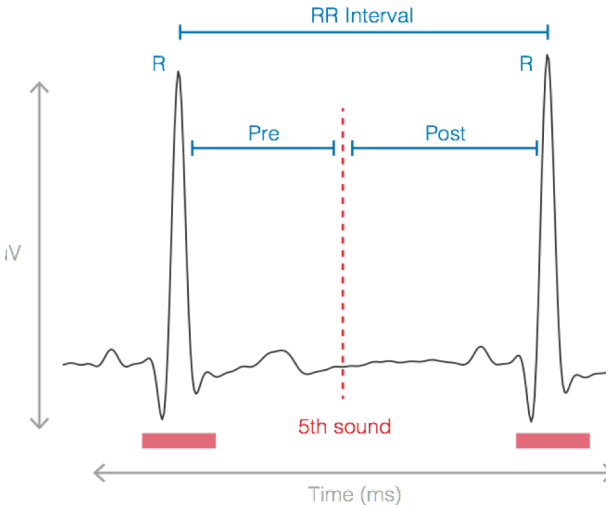
BRAIN



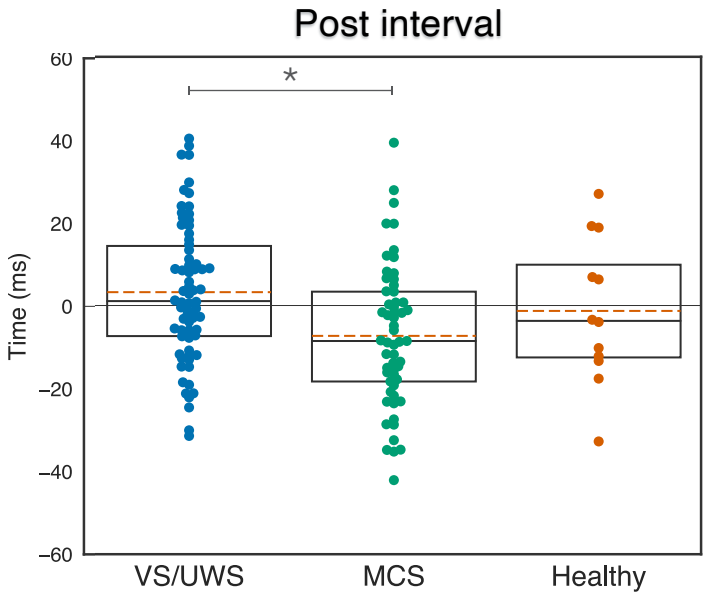
BRAIN-BODY INTERACTIONS

Cognition and somatic markers

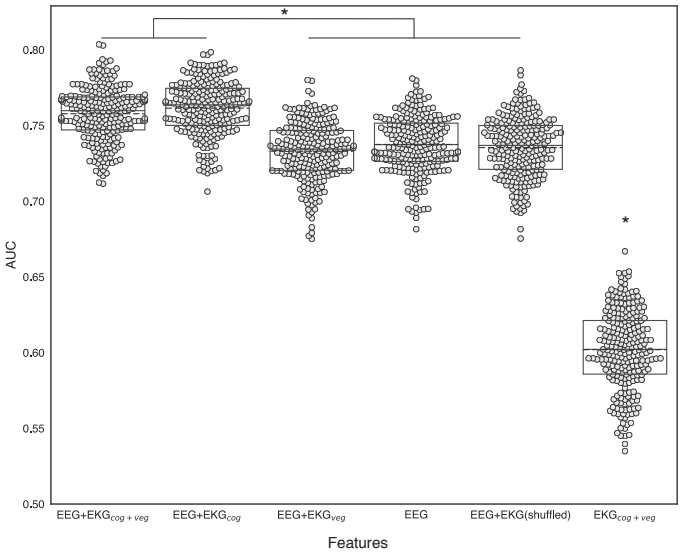
Auditory oddball paradigm



Cardiac cycle phase acceleration only in MCS



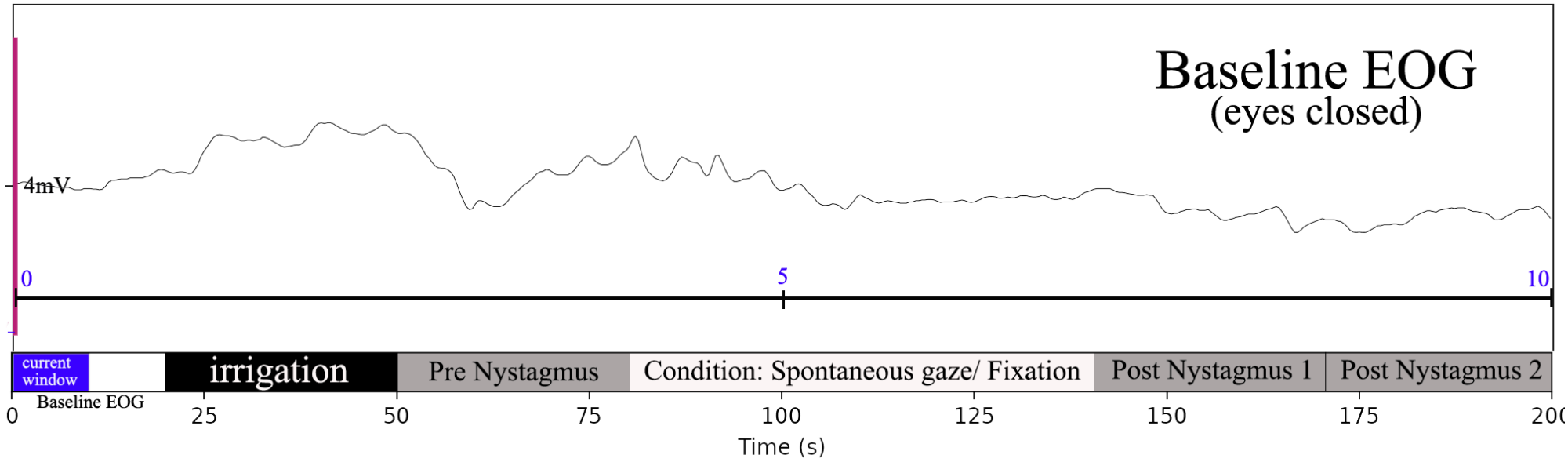
Electrocardiographic markers carry independent information from EEG

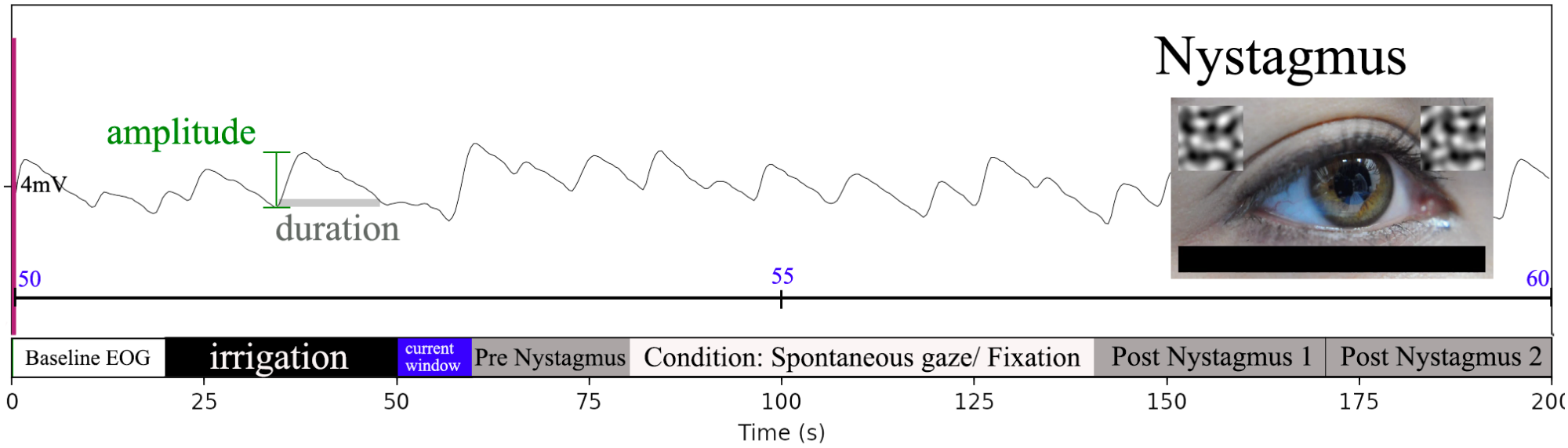


Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society
ANA AMERICAN NEUROLOGICAL ASSOCIATION

Federico Raimondo [1,2,3,4] Benjamin Rohaut, MD, PhD [5,6]
Athena Demertzi, PhD [3,5] Melanie Valente,[3,5] Denis A. Engemann [3,5,7,8]
Moti Salti, PhD,[9] Diego Fernandez Slezak, PhD,[1,2]
Lionel Naccache, MD, PhD,[3,4,5,6,10] and Jacobo D. Sitt, MD, PhD [3,5]

Warm water caloric irrigation





Conclusions

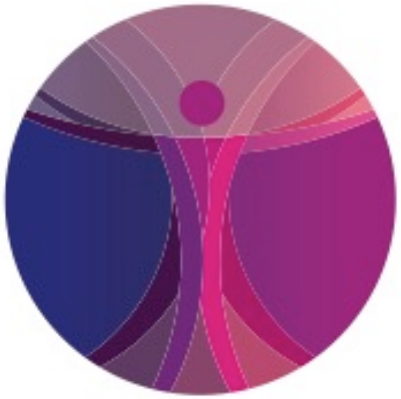
Consciousness needs a brain which:

- is intrinsically organized
- shows complexity
- shows dynamic flexibility

Consciousness from brain-body interactions

Consciousness as a collective consensus

Consciousness ….



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